are widely used by the pharmaceutical industry. However, they are not used for quantities larger than 150 kg because of handling problems with large bowls. Common designs such as the Hobart from Hobart Mfg. Co. (England) and N.V. Machines Collette (Belgium) are versatile and easy to install. Similar in principle but of more modern design are the Artofex mixers from Aesbach AG (Switzerland).

High-Shear Mixers

The first high-shear mixer to find widespread use in the pharmaceutical industry was the Lödige mixer. This mixer (Fig. 8a) is a horizontal cylinder equipped with a central shaft and plough shaped blades rotating at relatively high speeds, thus creating a highly intensive mixer action. In the early 1970s, the Diosna Pharmamixer was introduced. It was developed from mixers used in the plastic and dye industry where intensive mixing is required. Today, a number of similar high shear mixers are available, differing only in design details (Fig. 8b). Among others, Lödige MGT (Germany), Fielder Matrix (England), and Baker Perkins (England) range in capacities from 25 to 600 L. These mixer–granulators have been designed to take account of the special GMP requirements. Thus, clean lines, easy cleaning, and tight gland sealing are incorporated.

A totally different design is that of the Patterson-Kelly mixers (United States). They resemble Y-cone mixers and have a central shaft rotating at high speed. Changeable-bowl high shear mixers are available from N.V. Machines Collette (Belgium) and Aeromatic (Switzerland). Drive shafts to the impeller and chopper are taken through the top of the mixer, thus keeping the seals away from the product (Fig. 8c).

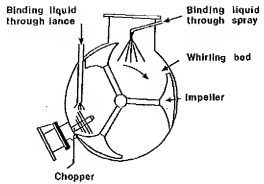
The major advantages of this type of mixer–granulators are the short processing times and their ability to function without the deaggregation and comminuting stages of wet granulation, thus reducing material handling. In recent years, attempts have been made to further develop high-shear mixer–granulators by the combination with vacuum drying and even fluidized-bed drying. The Fielder Pivor Processor [England], the Zanchetti & C. [Italy] Roto P granulator, and the Collette Topogranulator (Belgium) are designed for a one-step process by integrating loading, mixing, wet massing, drying, and sieving in a single vessel. In addition to reduced handling, these mixer–granulators offer advantages in the processing of toxic materials and, because of the temperature control, of heat-sensitive materials.

High-shear mixer-granulators have become widespread in the pharmaceutical industry because their operation is rapid and stable.

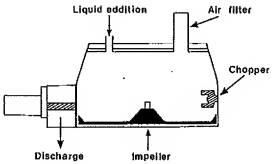
Fluidized-Bed Granulators

Plants for fluidized-bed granulation (Figs. 9 and 10) have been available to the pharmaceutical industry from Glatt (Germany) and Aeromatic (Switzerland) since the 1960s. This type of wet granulation has significant process advantages in reducing handling and contamination by dust. It is particularly suitable for automation.

a.



b.



c.

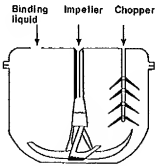


FIG. 8. Different types of high shear mixers; (a) horizontal mixer, (b) vertical mixer, (c) changeable-bowl mixer.

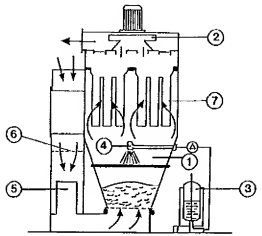


FIG. 9. Fluidized-bed granulator; (1) material container, (2) ventilator, (3) binder solution, (4) nozzle, (5) heating elements, (6) inlet air filter, (7) outlet air filter.

Continuous Granulation

Continuous granulation involves the use of a suitable device to continuously mix, wet mass, and discharge a granulation suitable for drying and subsequent handling. These continuous processes are usually associated with large tonnage. The first continuous mixer-granulators developed for the pharmaceutical industry by Schugi BV (Holland) and Patterson-Kelly (United States) were designed to produce up to 30,000 kg/h. In recent years, continuous mixer–granulators with capacities of several hundred kilogram per hour have become available, and can now be seen as an alternative to batch processing.

The Nica granulator (Sweden) operates by means of a continuous powder–liquid mixing device, capable of achieving a very uniform mix, producing a granulation that is transferred to a suitable drying unit. The capacity is up to about 600 kg/h. Another design incorporates extruders, which are made in three types:

- Screw extruders forcing the wetted mass through an aperture plate, for example the Buss Kneading-Extruder (Germany) and the Baker Perkins extruders (England) (Fig. 11)
- Roll extruders having a construction similar to that of roller compactors (Fig. 1), for example the Alexanderwerke Granulator (Germany) and the Hutt Extruder (Germany)
- Sieve extruders operating by forcing a wetted mass through a perforated plate by an oscillating arm

The benefits of continuous processes are primarily the flexibility of the batch size, elimination of scale-up, space savings, and reduction in labor costs. Limitations are that powders with poor flow properties give rise to difficulties in the feeding

EXHIBIT 1

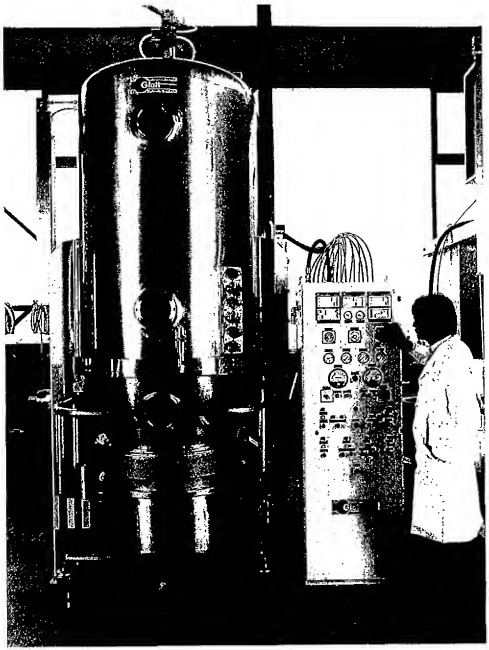


FIG. 10. Production-scale fluidized-bed granulator, Glatt WSG 120.